REMARKS

Claims 1, 8-16, 18-40 and 42-85 are currently pending in the application. Of these, claims 42, 56-59, 79 and 83-85 are withdrawn from consideration and claims 1, 8-16, 18-40 and 42-85 are subject to restriction and/or election.

Applicants have added claims 86-116 and canceled claims 1-85 without prejudice and without disclaimer with the right to refile the canceled claims in a separate application. Accordingly, claims 86-116 will be pending in the application upon entry of the amendments presented herein.

Election/Restrictions

Claims 56-59, 79, and 80-85 directed to an antibody are withdrawn from consideration because the Action takes the position that the originally filed claims were only to a GIP antagonist and that a related antibody is a distinct invention. The Examiner concludes that the originally presented invention has been constructively elected for prosecution. Applicants respectfully traverse and request reconsideration.

Applicants believe they can safely assume that the amino acid segments corresponding to positions 7-30 and 10-30 of SEQ ID NO:11 and SEQ ID NO:12, at least, are novel. Without belaboring the point, Applicants believe that they are entitled to claim a monoclonal antibody that recognizes the amino acid sequence of SEQ ID NO:5

Accordingly, Applicants respectfully submit antibody claims and request reconsideration of the restriction. In the event the Examiner declines to examine the claims, Applicants request withdrawal of the claims without prejudice with right to cancel and refile in a subsequent application.

Objection to the Specification

The previously filed amendment to add the 60/032329 prior-filed application has been objected to as improperly incorporating the application by reference. Applicants have amended the language.

Objections to the Claims

Claim 68 is objected to for being of improper dependent form. Applicants have cancelled claim 68, making the rejection moot.

Claim Rejections under 35 U.S.C. §101

Claims 1, 8-14, 18-21, 39, 40, 43,44, 50, 52-55, 60,67-78, and 80-82 are rejected under 35 U.S. C. §101 because the invention is allegedly directed to non-statutory subject matter because the claims are not written to clearly distinguish the compounds from natural products. Applicants' new claims take into account the Examiner's suggestion to identify the compounds as "isolated".

Maintained Claim Rejections Under 35 U.S.C. §112, First Paragraph

Claims 27-30, 35, 36 and 39 remain rejected under 35 U.S.C. §112, first paragraph as containing subject matter not sufficiently described in the specification to reasonably convey to one skilled in the relevant art that the inventors had possession of the invention at the time the application was filed, which the Examiner states is a new matter rejection. The Examiner alleges that certain limitations cannot be found in the specification or original claims, including a polypeptide that interferes with GIP biological activity where the polypeptide comprises amino acid sequences 16-30, 21-30 or 7-9 of GIP.

Additionally, the new matter rejection has also been applied to claims 1,9,12, 13, 18, 20, 24-25, 27-32, 34-43, 52-55, 63, 68, 70, 75-76 and 80-82. The Examiner admits that the disclosure supports a GIP or GIP receptor antagonist directed to amino acids 7-30 or 10-30 of GIP, but takes the position that there is no support for the 95% identity of active

segments, the unacceptable weight gain or the limitations in claims 63,68, 70, 75-76 or 80-82.

Claims 8,11,15 and 16 are rejected under 35 U.S.C. 112, first paragraph for allegedly lacking enablement for other than antagonists consisting essentially of amino acids 7-30 or 10-30 of rat GIP, while admittedly being enabled for these segments. The Action appears to reject the scope of these claims.

The Action further alleges that an enablement rejection applies to claims 14, 22, 27-30, 35-39, 43-55, 60-78 and 80-82. The Action takes the position that in reference to sequences 2,5,8 and 10, there is not a reasonable correlation to four, highly similar antagonistic peptides that differ only in a single amino acid. In short, the Examiner states that the issue is one of breadth because the number of working examples does not support predictability of antagonistic activity.

In discussing the basis for the enablement (scope) rejections, the Action takes the position that protein structure is unpredictable and complex and that insufficient information has been provided by Applicants in terms of number of examples or identification of active site in the amino acid segments that are antagonists of GIP receptor.

The Examiner indirectly admits that many amino acid substitutions are generally possible in any given protein with reasonable expectation of success but further asserts that some positions in the sequence are "critical" to function, such as regions directly involved in binding. The Examiner has concluded that there is no guidance in the specification to determine what positions are tolerant to change, despite adequate specification for producing and screening active antagonists.

The Action implies that even if an active or binding site is identified, it could not be assumed that such a site would assume the proper three-dimensional configuration to be active. Because conformation is dependent upon surrounding residues, the substitution of non-essential residues can destroy activity. In conclusion, the Examiner takes the

position that undue experimentation would be required to make and use the invention as broadly claimed.

Applicants respectfully disagree, and request that the Examiner take the following comments into consideration as support for the cancelled set of claims, and also for the new claims which are believed to be fully supported in the specification and by knowledge available to those skilled in the art at the time the application was filed.

Applicants' Support for Claims

Claims 52, 54, and 55, according to the Action, "require identity to only a single amino acid residue." Applicants apologize for this misconception as they had intended 95% identity to mean 95% of corresponding positions are the same as the active segment for the same length segment. This would mean that only a single residue is different and certainly this would not lead to undue experimentation with the limited number of substitutions that could be made in the short segments disclosed. Applicants have clarified the language in the new claims and believe that such claims are not directed to a large number of sequences. Applicants believe that undue experimentation does not apply to the new claims.

Applicants would also like to point out that the invention is focused on short amino acid segments that are derived from a 42-residue polypeptide (SEQ ID NO:11 and SEQ ID NO:12) that binds to the GIP receptor. Certainly for some large proteins, the substitution of a single amino acid would generate thousands of residues. The Action's general statements may in some cases apply to higher molecular weight, longer chain proteins with complex β-sheet, α-helix and loop structures. The 7-30 and 10-30 amino acid segments in the present application have no disulfide bonds, no quaternary structure (because there is only a single short residue), are expected to have minimal tertiary structure and only some secondary structure, probably α -helix, although β -sheets can form with as few as 6 residues. Most of the amino acids in SEQ ID NO: 5 are neutral amino acids and would be expected by one skilled in the art to be readily substituted with equivalents without loss of activity.

Moreover, as admitted by the Examiner, equivalent substitutions are well-known. Studies have revealed that proteins are generally tolerant of amino acid substitutions with recognition of which substitutions are permissive at a selected position of the protein. Recognized conservative substitutions among aliphatic amino acids include Ala, Val, Leu and Phe; Asn and Gln as exchangeable amides; basic residue Lys and Arg; hydroxyl residues Ser and Thr; aromatic residues Phe and Tyr; and acidic residues Asp and Glu. Substitutions are not limited to conservative changes; however, there is generally a greater expectation of similar function and activity than with non-conservative changes. In fact, equivalent changes are recognized in the following groups: (1) Lys, Arg, His (2) Phe, Tyr, Trp, His, (3) Ala, Pro, Gly, Glu, Asp, Gln, Asn, Ser, Thr and (4) Cys, Ser, Tyr, Thr, and (5) Val, Ile, Leu, Met, Ala, Phe.

Applicants' assertions are supported by the Bowie, *et al.* reference (Science, vol. 247, 1306-1310, 1990). The authors report that "...proteins are surprisingly tolerant of amino acid substitutions..." (page 1306, col 2, 2nd paragraph). While recognizing that there are constraints and some unpredictability in protein activity and structure when substitutions are made, applicants believe that it was well-known in the art at the time the application was filed that conservative changes could be made with the expectation of finding (testing) some activity similar to the parent sequence.

Applicants' specification provides evidence that such substitutions can provide functional equivalency. The rat sequence and the human GIP sequences differ only at a single position where His is replaced by Arg. It is believed that with respect to SEQ ID NO:5, the skilled practitioner could make at least a single conservative substitution in the short polypeptide with expectation of obtaining a polypeptide with similar activity.

Applicants have not ignored the question of what parts of the claimed sequences are important in preparing GIP antagonists; i.e., "Thus, peptide antagonists would appear to require the segment from amino acids 7-9 (SEQ ID NO:6) of the GIP sequence, and some or all of the amino acids from 10-30 (SEQ ID NO:5 and SEQ ID NO:10) or effective

alternative amino acids thereto are likely to promote binding to the receptor." (page 8, last four lines in [0033]. In [0034] Applicants point out that "...any polypeptide sequence which effectively prevents GIP activation of its native receptor, such as the sequence containing amino acids in positions 7-30 of GIP sequence (SEQ ID NO:2 and SEQ ID NO:8) that include additional, deleted or alternative amino acids to form an effective GIP polypeptide antagonist. Polypeptides based on this sequence may be designed for use as GIP antagonists according to this invention by the skilled artisan, who will routinely confirm that the resultant peptides exhibit antagonist function by testing the peptides in vitro and in vivo assays such as those described in Examples 1 and 3-5 below."

Applicants are not claiming an unduly large number of effective polypeptides; rather, they are claiming those that would reasonably have the claimed activity based on the limited number of substitutions the skilled practitioner would recognize from the state of the art and the guidance provided in the specification. Applicants contend that IN THIS CASE with the guidance from the specification, that the nature of this invention is not too complex, that there is guidance in the specification to identify structural features required for activity, that the working examples are not too limited, and that the state of the art does establish some predictability of the effects of mutation on structure and function of this polypeptide. Applicants' claims, as currently presented, are not unduly broad and would not require undue experimentation of the skilled artisan.

Accordingly, without acceding to the Action's assertions that there is insufficient guidance in the specification to make and use the invention, Applicants have presented a new set of claims that are directed to one of the species acknowledged as supported in the original disclosure. Applicants respectfully disagree that there is no support in the specification for other than two of the GIP peptides of the several that were described. However, in the interest of expediting prosecution, Applicants submit a new set of claims focused on GIP active SEQ ID NO:5 (the 10-30 segment).

Claim Rejections Under 35 U.S.C. §102

Claim 44 is rejected under 35 U.S.C. 102(b) as anticipated by Ebert, allegedly teaching a specific GIP antiserum, a pharmaceutical composition comprising the anti-GIP, antagonistic antibody or antibodies.

Claim 44 has been replaced with claims 111-116. Applicants respectfully request reconsideration of this rejection because the claim is directed to a monoclonal antibody directed toward a novel sequence. It is different from the polyclonal antiserum described in the Ebert reference.

New Claims rejections under 35 U.S.C. §112, First Paragraph

Claims 8, 11, 14-16, 22, 44-51, 60-65, 70-78 and 80-82 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement such as not to reasonably convey to one skilled in the art that the inventors had possession of the invention at the time the application was filed. The claims are directed to a genus of compounds that are GIP antagonists, allegedly encompassing any and all compounds possessing the desired functional activity. In general, the Examiner takes the position that the specification does not indicate what distinguishing characteristics are shared by members of the claimed genus and does not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions so that numerous structural variants are included. It is asserted that the genus is highly variant and that the 7-30 and 10-30 sequences are not sufficient to describe the genus. Applicants respectfully disagree.

As discussed, Applicants submit that the claims are not directed to unduly broad subject matter and that the indicated substitutions would not be expected to significantly alter the activity of the parent sequence. It is believed that those skilled in the art would recognize and have a reasonable expectation of such activity, based on the demonstrated activity of the parent, the means for testing activity, the limited number of compounds, the

identification of the general regions of the sequence that contribute to antagonist activity, and the guidance provided throughout the specification.

In the interest of expediting prosecution, Applicants have cancelled claims 8, 11, 14-16, 22, 44-51, 60-65, 70-78 and 80-82 solely in order to expedite prosecution. The added claims are believed to be fully supported, as discussed. Applicants reserve the right to pursue the canceled claims filed in this application or in one or more separate applications.

Claims rejections under 35 U.S.C. §112, Second Paragraph

Claims 22, 23-38, 53, 65, 70, 80-82, 47, 61-65, 67, 70, 8076, 66 and 66-69 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Generally, the Action suggests that "isolated" should be added to claims 22, 23-38 to correct antecedent basis. This term is found in the new claims.

"95% identity to a group" is said not to be clear. This term has been clarified in the new claims.

The term "unacceptable" in claims 65, 70, 80-82 is not used in the new claims. The term "normally achieved", "normally attained", or "abnormal" in claims 47, 61-65, 67, 70 or 80 is not used in the new claims. The term "non-homologous" in claim 76 has not been used in the new claims.

Identification of "amino acids 10-30 from SEQ ID NO:10" has not been used in the new set of claims.

Claims 66-69 are allegedly indefinite for recitation of "comprises amino acids identical to". While Applicants believe an identical amino acid is a clear concept, more definite

language has been employed in the new set of claims to indicate that the additional sequences are of the indicated length.

Applicants submit that with the cancellation of the recited claims, the rejection for lack of clarity is overcome; and does not apply to the new set of claims. Applicants respectfully request removal of the rejection.

Double Patenting

Claims 27, 35, 36 and 13 are identified by the Examiner as being substantial duplicates of claims 28, 37, 38 and 20 respectively and will be objected to under 37 CFR 1.75 if found allowable. Applicants acknowledge the Examiner's notification.

Claims 1,8-16, 18-40, 43-55, 60-78, and 80-82 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 10/003674.

Applicants understand that this is a provisional rejection as the conflicting claims have not in fact been patented. Applicants reserve the right to respond as such time as is appropriate.

Supplemental Information Disclosure Statement

Applicants submit concurrently herewith a Supplemental Information Disclosure Statement for the Examiner's information and respectfully request that the cited references be made of record. Copies of the cited references are included.

CONCLUSION

Applicants believe that all formalities have been complied with and a complete response has been submitted. It is respectfully submitted that this application is now in condition for allowance with claims 86-118. Should any issues remain or should the Examiner believe that a telephone conference with Applicants' attorney would be helpful in

expediting prosecution of this application, the Examiner is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,

Date: January 26, 2005

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